

# Exercise Oscillatory Ventilation May Predict Sudden Cardiac Death in Heart Failure Patients

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## Objectives

The purpose of this study was to test the ability of cardiopulmonary exercise testing (CPET)-derived variables as sudden cardiac death (SCD) predictors.

## Background

The CPET variables, such as peak oxygen uptake ( $\text{VO}_2$ ), ventilatory requirement to carbon dioxide ( $\text{CO}_2$ ) production ( $\text{VE}/\text{VCO}_2$ ) slope, and exercise oscillatory breathing (EOB), are strong predictors of overall mortality in chronic heart failure (CHF) patients. Even though up to 50% of CHF patients die from SCD, it is unknown whether any of these variables predicts SCD.

## Methods

One hundred fifty-six CHF patients (mean age:  $60.9 \pm 9.4$  years; mean ejection fraction:  $34.9 \pm 10.6\%$ ) underwent CPET. Subjects were tracked for sudden versus pump-failure cardiac mortality over  $27.8 \pm 25.2$  months.

## Results

Seventeen patients died from SCD, and 17 died from cardiac pump failure. Survivors showed significantly higher peak  $\text{VO}_2$  ( $16.8 \pm 4.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and lower  $\text{VE}/\text{VCO}_2$  slope ( $32.8 \pm 6.4$ ) and prevalence of EOB (20.3%), compared with subjects who experienced arrhythmic ( $13.5 \pm 3.2 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ;  $41.5 \pm 11.4$ ; 100%) or nonarrhythmic ( $14.1 \pm 4.7 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ;  $38.1 \pm 7.3$ ; 47.1%) deaths ( $p < 0.05$ ). At Cox regression analysis, all variables were significant univariate predictors of both sudden and pump failure death ( $p < 0.01$ ). Multivariate analysis, including left ventricular (LV) ejection fraction, LV end systolic volume, and LV mass selected EOB, was the strongest predictor of both overall mortality (chi-square: 38.7,  $p < 0.001$ ) and SCD (chi-square: 44.7,  $p < 0.001$ ), whereas  $\text{VE}/\text{VCO}_2$  slope was the strongest ventilatory predictor of pump failure death (chi-square: 11.8,  $p = 0.001$ ).

## Conclusions

Exercise oscillatory breathing is an independent predictor of SCD in patients with CHF and might help as an additional marker for prioritization of antiarrhythmic strategies. (J Am Coll Cardiol 2007;50:299–308) © 2007 by the American College of Cardiology Foundation

Up to 50% of total mortality in patients with chronic heart failure (CHF) is attributable to sudden cardiac death (SCD). Selection of those who exhibit an increased risk of SCD and prioritization to treatments with effective impact on mortality, such as implantable cardioverter-defibrillator (ICD) therapy, are highly advocated (1). Nonetheless, the indiscriminate use of ICDs is an economically costly undertaking (1,2), and patients with negligible risk of SCD might be exposed to the potential risks of invasive procedures without benefit. In this subset of patients, the ICD will not improve overall mortality but has the potential to hasten

death and negatively impact quality of life (2). Therefore, subcategorizing of risk stratification with regard to sudden and pump failure death is of essential impact for clinical decision-making, and identification of markers predictive of risk of death for a specific cause remains a relevant challenge (1,3). A considerable number of cardiopulmonary exercise testing (CPET)-derived variables provide basic prognostic information in patients with CHF of different severity (4–6). Among others, oxygen consumption at peak exercise (peak  $\text{VO}_2$ ) (7,8) and abnormalities in exercise ventilation such as an excessive ventilatory requirement/carbon dioxide production rate ( $\text{VE}/\text{VCO}_2$ ) and peculiar patterns of exercise oscillatory breathing (EOB) have gained a primary role as reference markers of total mortality in CHF patients with either left ventricular (LV) systolic (9–16) or diastolic dysfunction origin (17). Despite this evidence, no study has, to the best of our knowledge, been focusing on the potential validity of these variables in the prediction of SCD. This seems to be an interesting issue mainly concerning the

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## Abbreviations and Acronyms

<b>CI</b> = confidence interval
<b>CPET</b> = cardiopulmonary exercise test
<b>EF</b> = ejection fraction
<b>EOB</b> = exercise oscillatory breathing
<b>ICD</b> = implantable cardioverter-defibrillator
<b>LV</b> = left ventricle/ventricular
<b>RER</b> = respiratory exchange ratio
<b>ROC</b> = receiver-operating characteristic
<b>SCD</b> = sudden cardiac death
<b>VCO<sub>2</sub></b> = carbon dioxide production
<b>VE</b> = ventilation
<b>VO<sub>2</sub></b> = oxygen uptake

relevant pathogenetic mechanisms that sustain exercise intolerance in CHF patients and the neural instability—such as an impaired central and peripheral chemoreflex control of ventilation—that underlies abnormalities in ventilation (18,19). Accordingly, the aim of the present study was to test whether and which exercise CPET-derived variables predict an increased burden of risk for SCD.

## Methods

**Subject characteristics.** One hundred and fifty-six patients with compensated CHF were enrolled in this study. All were optimally managed from a pharmacologic standpoint before initiation of the study.

**Echocardiography.** Standard M-mode and 2-dimensional echocardiography and Doppler blood flow measurements were performed in agreement with the American Society of Echocardiography Guidelines (20). Septal and posterior LV wall thickness was obtained from the parasternal long-axis view. The LV end-systolic and -diastolic volumes were obtained from 2-dimensional apical images. The LV ejection fraction (EF) was calculated according to Simpson's method from 2-dimensional apical images.

The LV mass was calculated according to the formula proposed by Devereux et al. (21).

Pulsed wave Doppler echocardiography was used to assess: mitral peak early (E) and late (A) wave flow velocity and E wave deceleration time. Isovolumic relaxation time (IVRT) was also determined.

**CPET.** Each patient performed a supervised, standard, progressively increasing (personalized ramp protocol) work rate CPET to maximum tolerance on an electromagnetically braked cycle ergometer at baseline and during the follow-up assessments. The aim was to achieve peak exercise in approximately 10 min. If test duration was >12 min or <8 min, the test was repeated the next day with the work rate increase adjusted as needed. Ventilatory expired gas analysis was obtained with a metabolic cart (Medgraphics CPET-D, Minneapolis, Minnesota). The oxygen and carbon dioxide sensors were calibrated before each test with gases with known oxygen, nitrogen, and carbon dioxide concentrations. The flow sensor was also calibrated before each test with a 3-l syringe. Monitoring consisted of continuous 12-lead electrocardiography, manual blood pressure measurements every stage, heart rate recordings every stage via the electrocardiogram, and rating of perceived exertion (Borg 15 grade scale) each stage. Test termination criteria consisted of patient request, ventricular tachycardia, ≥2 mm of horizontal or downsloping ST-segment depression, or a drop in systolic blood pressure ≥20 mm Hg during exercise. A qualified exercise physiologist with physician supervision conducted each tests.

The VO<sub>2</sub> (ml·kg<sup>-1</sup>·min<sup>-1</sup>), VCO<sub>2</sub> (l·min<sup>-1</sup>), and VE (l·min<sup>-1</sup>) were collected throughout the exercise test. Peak

**Table 1** Baseline Characteristics

	All Patients (n = 156)	Survivors (n = 122)	Nonsurvivors (n = 34)	
			SCD (n = 17)	Pump Failure (n = 17)
Age, yrs	60.9 ± 9.4	60.4 ± 9.9	63.2 ± 7.2	62.3 ± 7.6
Gender, M/F	125/31	95/27	17/0	13/4
Etiology, ischemic/nonischemic	98/58	76/46	9/8	13/4
NYHA functional class, I/II/III/IV	38/73/38/7	37/61/23/1	0/5/7/5	1/7/8/1
Mean ± SD	2.1 ± 0.81	1.9 ± 0.72*	3.0 ± 0.79	2.5 ± 0.72
<b>Echocardiography</b>				
LVEF, %	34.5 ± 10.6	36.1 ± 9.7	25.2 ± 6.3†	34.9 ± 10.6
LVESV, ml	107 ± 63	95 ± 64	118 ± 50‡	105 ± 48
LVEDV, ml	184 ± 64	145 ± 75*	195 ± 60	190 ± 64
LV mass, g	225 ± 80	215 ± 70	260 ± 60‡	235 ± 70
E/A ratio	1.9 ± 0.5	1.7 ± 0.5*	2.2 ± 0.35	2.3 ± 0.32
IVRT, ms	103 ± 34	104 ± 30	92 ± 30†	100 ± 25
DT, ms	220 ± 70	246 ± 73	150 ± 70†	165 ± 78
<b>Therapy distribution</b>				
ACE inhibitor	76%	79%	65%	70%
Anti-aldosterone	39%	32%*	59%	65%
Beta-blocker	46%	46%	34%†	59%

\*Survivors significantly more than sudden cardiac death (SCD) and pump failure groups (p < 0.05). †SCD group significantly less than survivors and pump failure group (p < 0.05). ‡SCD group significantly more than survivors and pump failure death group (p < 0.05).

ACE = angiotensin-converting enzyme; DT = deceleration time; E/A = early to late ventricular filling; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; IVRT = isovolumic relaxation time; LV = left ventricular; NYHA = New York Heart Association.

**Table 2** CPET Data

	All Patients (n = 156)	Survivors (n = 122)	Nonsurvivors (n = 34)	
			SCD (n = 17)	Pump Failure (n = 17)
Peak $\text{VO}_2$ , $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$	16.6 ± 4.6	16.8 ± 4.5*	13.5 ± 3.2	14.1 ± 4.7
VE/ $\text{VCO}_2$ slope	34.5 ± 7.9	32.8 ± 6.4†	41.5 ± 11.4	38.1 ± 7.3
Peak RER	1.01 ± 0.13	1.00 ± 0.12‡	1.03 ± 0.17	1.09 ± 0.08
Peak Pet $\text{CO}_2$ , mm Hg	33.2 ± 5.4	34.0 ± 5.4*	30.4 ± 5.0	31.1 ± 4.5
EOB, %	33	22†	100§	47
VE/ $\text{VCO}_2$ slope ≥37.0, %	34	26†	59	65
Peak $\text{VO}_2$ ≤14.4 $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ , %	39	33‡	71	53

\*Survivors significantly more than sudden cardiac death (SCD) and pump failure death group ( $p < 0.05$ ). †Survivors significantly less than SCD and pump failure death group ( $p < 0.01$ ). ‡Survivors significantly less than SCD group ( $p < 0.05$ ). §SCD group significantly more than pump failure death group ( $p < 0.01$ ).

CPET = cardiopulmonary exercise test; EOB = exercise oscillatory breathing; Pet $\text{CO}_2$  = end-tidal of carbon dioxide; RER = respiratory exchange ratio; VE/ $\text{VCO}_2$  = ventilation to  $\text{CO}_2$  production;  $\text{VO}_2$  = oxygen uptake.

$\text{VO}_2$  was expressed as the highest 30-s average value obtained during the last stage of the exercise test. Peak respiratory exchange ratio (RER) was the highest 30-s averaged value during the last stage of the exercise test. Ten-second averaged VE and  $\text{VCO}_2$  data, from the initiation of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, Washington) to calculate the VE/ $\text{VCO}_2$  slope via least squares linear regression ( $y = mx + b$ ,  $m = \text{slope}$ ).

**EOB definition.** The EOB was assessed with the criteria previously reported by Leite et al. (15). Specifically, EOB was defined according to the following criteria: 1) 3 or more regular oscillatory fluctuations in VE; 2) minimal average amplitude of ventilatory oscillation of 5 l (peak value – the average of 2 in-between consecutive nadirs); and 3) a regular oscillation as defined by an SD of 3 consecutive cycle lengths (time between 2 consecutive nadirs) within 20% of the average.

**Mode of death.** Subjects were followed for cardiac-related mortality via medical chart review. Cause of cardiac-related death was also determined, and death was classified as sudden death, pump failure, or resulting from other causes. All deaths were reviewed, and probable cause was established by a committee of 3 physicians after a review of hospital records, autopsy findings, death certificates, and interviews with family members. Sudden death was defined as witnessed cardiac arrest or death within 1 h after the onset of acute symptoms or unexpected, unwitnessed death (i.e., during sleep) in a patient known to have been well within the previous 24 h (22). Deaths resulting from CHF deterioration with progression of congestive symptoms were classified as pump failure. Patients in whom mortality was of a noncardiac etiology were treated as censored cases.

**Statistical analysis.** One way analysis of variance was used to compare continuous variables amongst survivors, the SD group, and the pump failure death group. Tukey's test for multiple comparison was used when a significant difference was detected. Chi-square analysis was used to assess differences in categorical variables amongst the 3 groups. Receiver-operating characteristic (ROC) curves were constructed for peak  $\text{VO}_2$ , the VE/ $\text{VCO}_2$  slope, and EOB to

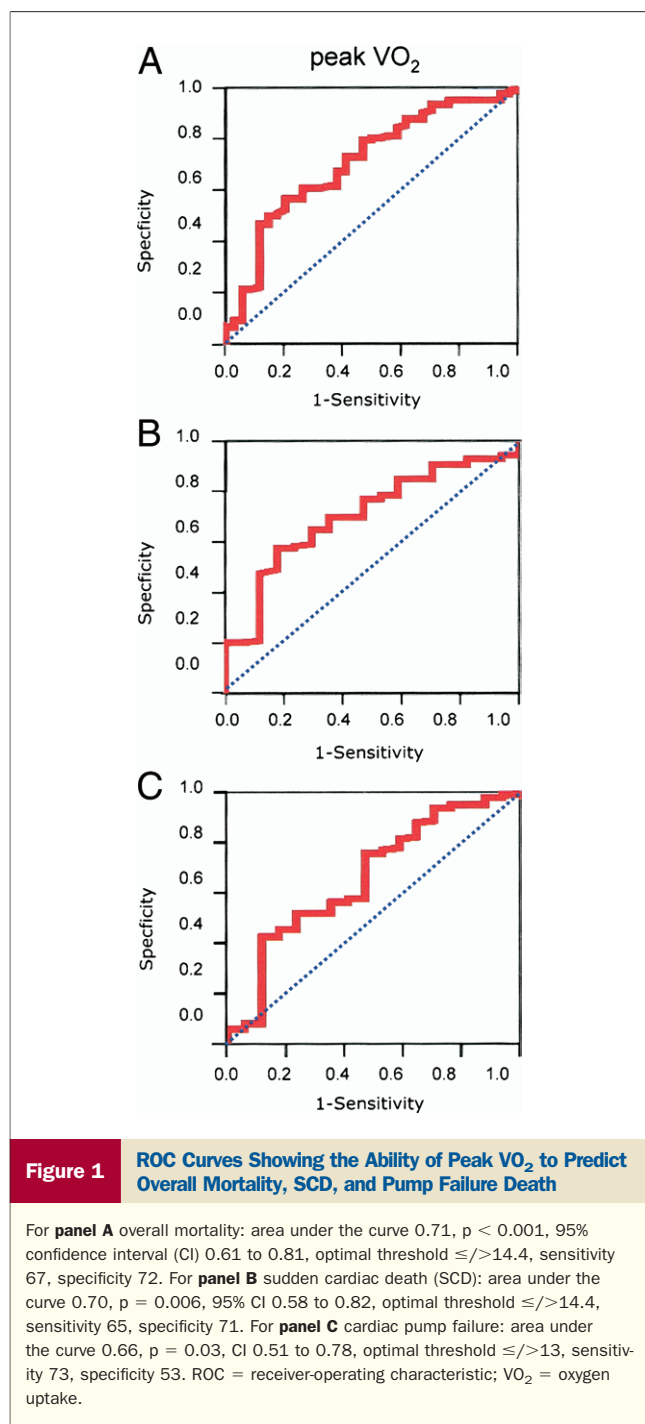
determine the optimal prognostic threshold value (highest combination of sensitivity/specificity) for overall, arrhythmia, and nonarrhythmia related death. Univariate Cox regression analysis assessed the ability of peak  $\text{VO}_2$ , the VE/ $\text{VCO}_2$  slope, and EOB along with LVEF, LVESV, and LV mass to predict overall cardiac mortality as well as arrhythmia (nonarrhythmia-related death treated as censored cases) and nonarrhythmia (arrhythmia related death treated as censored cases) related death. Threshold values determined by ROC curve analysis for peak  $\text{VO}_2$  and the VE/ $\text{VCO}_2$  slope were used in the Cox regression analyses. The forward stepwise method was used for the multivariate analyses with entry and removal  $p$  values set at 0.05 and 0.10, respectively. Kaplan Meier analysis was used to assess differences in cardiac-related events with variables retained in the multivariate Cox regression analysis. The log-rank test was used to determine whether the difference in event-free survival was significant between subjects falling into different categories. All data are reported as mean values ± SD. Statistical differences with a  $p$  value < 0.05 were considered significant.

## Results

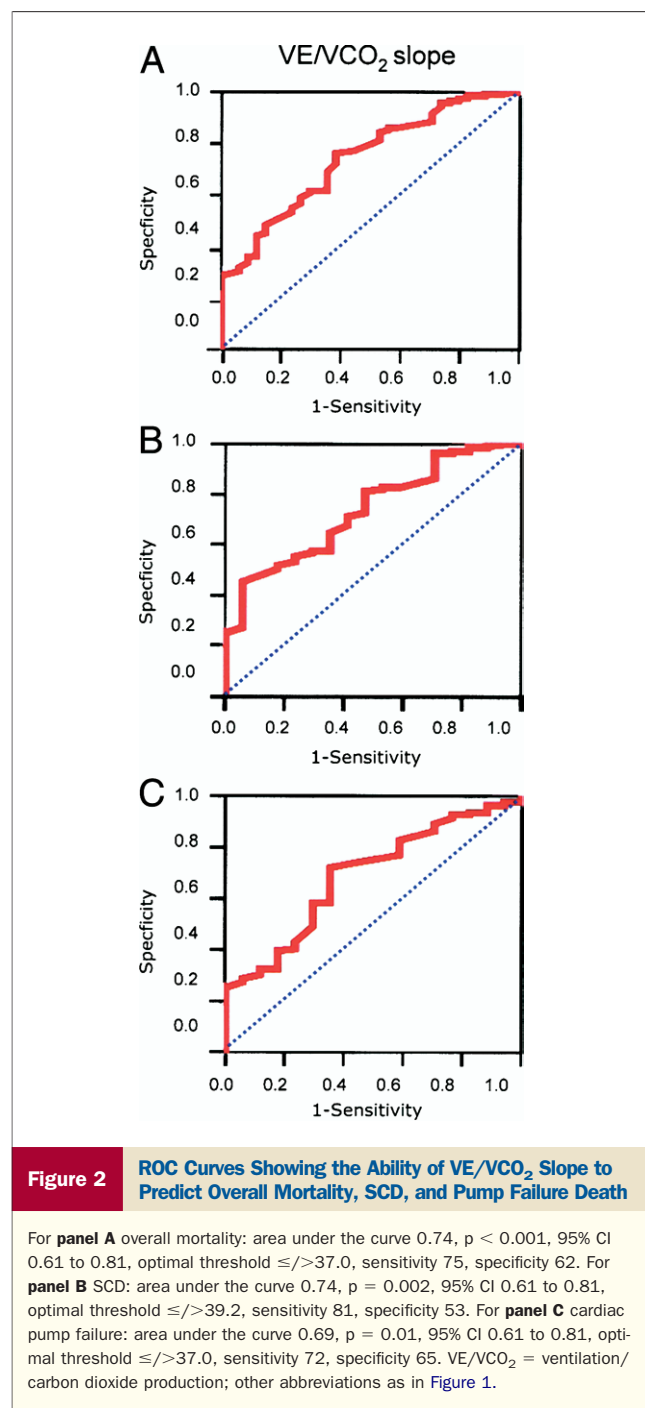
The mean tracking period was  $23.6 \pm 18.0$  months. Thirty-four subjects died from cardiac causes during the 4-year tracking period. The annual mortality rate was 9.6%. Seventeen deaths were due to SCD, whereas the remaining 17 were secondary to pump failure. No patients were lost to follow-up. Twelve patients had ventricular fibrillation successfully terminated by the ICD. Seven patients underwent heart transplantation.

**Patients' characteristics according to clinical outcome.** Patient characteristics according to the clinical outcome are given in Table 1. Left ventricular ejection fraction was significantly lower in the SCD group compared with survivors and the pump failure death group. In SCD patients LVESV, LVEF, and LV mass were significantly greater than in survivors and in those dying because of pump failure.

New York Heart Association (NYHA) functional class was significantly lower in survivors compared with the SCD



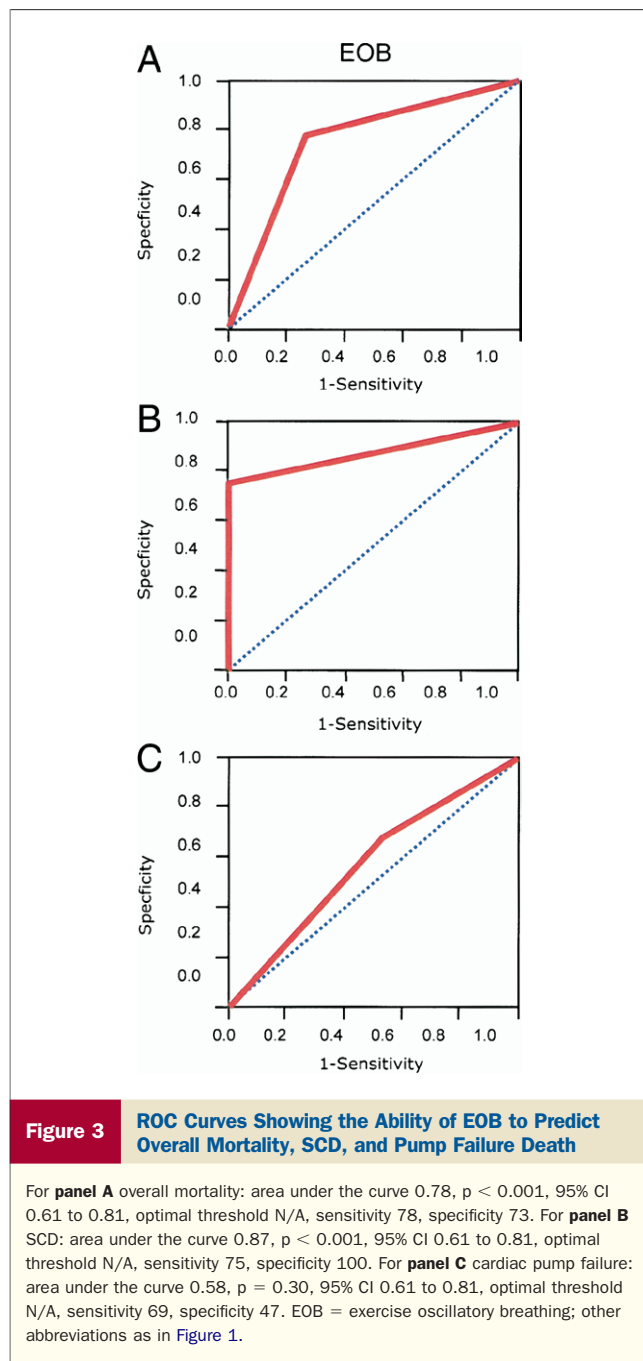
and pump failure group. Lastly, there were significant differences in the number of subjects receiving antialdosterone and beta-blocking agents amongst the 3 groups. Exercise test results are presented in Table 2. Peak  $\text{VO}_2$  was significantly greater and the  $\text{VE}/\text{VCO}_2$  slope and EOB prevalence were significantly lower in survivors compared with the other groups. Peak RER was significantly lower in survivors compared with the pump failure death group. Although peak  $\text{VO}_2$  and the  $\text{VE}/\text{VCO}_2$  slope were not significantly different between the arrhythmia and non-



arrhythmia groups, prevalence of EOB was greater in SCD patients (100% vs. 47.1%;  $p < 0.01$ ).

Receiver-operating characteristic curve analysis for each ventilatory variable according to overall mortality, SCD, and pump failure mortality are reported in Figures 1, 2, and 3, respectively. Results of ROC curve analysis for LV mass, LVESV, and LVEF are presented in Table 3. Peak  $\text{VO}_2$  and the  $\text{VE}/\text{VCO}_2$  slope classification schemes were significant for all 3 scenarios. The EOB classification scheme was significant for overall cardiac mortality and arrhythmia-related mortality only. The area under the curve was greatest





for EOB for the overall cardiac mortality and arrhythmia-related mortality classification schemes. The area under the curve was greatest for the VE/VCO<sub>2</sub> slope for nonarrhythmia-related mortality.

**Predictors of mortality.** Univariate predictors of death are reported in Table 4. At univariate analysis, all CPET variables of interest along with cardiac function parameters were significant predictors of overall cardiac mortality, SCD mortality, and pump failure mortality. However, as to CPET variables, EOB performed somewhat better than VE/VCO<sub>2</sub> slope and peak VO<sub>2</sub>. Analyses of the Kaplan-Meier survival curves revealed a 4-year total cardiac mortal-

ity survival rate of 100% for those with no EOB compared with only 67.3% for those with EOB (Fig. 4). An even worse survival rate was observed when considering SCD mortality group (51.9%) (Fig. 5) for patients exhibiting EOB. The worse 4-year Kaplan-Meier survival rate in the pump failure mortality group was observed for patients with VE/VCO<sub>2</sub> slope  $\geq 37$  (Fig. 6).

**Multivariate Cox regression analysis.** Multivariate Cox proportional hazards model analyses for different causes of death are reported in Table 5. The EOB was the strongest predictor of overall and SCD mortality, whereas VE/VCO<sub>2</sub> slope maintained a predictive value as to overall cardiac mortality and pump failure death outperforming EOB as predictor of pump failure mortality. Remarkably, peak VO<sub>2</sub> did not emerge as a predictor independently of type of cardiac death considered.

As to cardiac function, LVEF did not emerge as a predictor of any end point; LV mass showed a high prognostic predictivity for overall cardiac mortality, SCD, and pump failure death. The LVESV strongly predicted pump failure death and not SCD.

## Discussion

Direct comparison among recognized prognostic CPET-derived variables has shown EOB as the only independent predictor of SCD. The information is novel. It expands the mounting clinical and prognostic relevance provided by CPET and strengthens the importance of critically interpreting exercise ventilatory abnormalities in the follow-up of CHF patients. In this respect, occurrence of exercise oscillatory gas exchange kinetics seems worth taking into account as a potential additional marker for potential prioritization to ICD therapy.

**CPET variables and prediction of mode of death.** Peak VO<sub>2</sub> is an established prognosticator in patients with advanced CHF (7) independently of beta-blocker use (8) and remains the only noninvasive variable that represents an absolute key indication to list for heart transplantation (23). In recent years, 2 variables have been progressively attracting the interest and, especially in patients with intermediate exercise performance, have proven to be superior to peak VO<sub>2</sub>: 1) the increased slope of VE/VCO<sub>2</sub> production (9–14); and 2) the oscillatory kinetics in expired gases and ventilatory response to incremental exercise (15,16,24). Interestingly enough, the respective predictive ability of these variables in the definition of mode of death has not been previously investigated, and studies performed on large patient populations have focused on the CPET variables' prediction of overall cardiac and/or total mortality, without providing insights into the mode of death (4–18).

In the present investigation, all CPET variables were predictive of overall cardiac mortality, with EOB performing better than peak VO<sub>2</sub> and VE/VCO<sub>2</sub> slope. However, clear differences in the predictive accuracy have emerged

**Table 3** ROC Curve Results

	ROC Area	p Value	95% CI	Optimal Threshold	Sensitivity/Specificity
Overall cardiac mortality					
LV mass, g	0.66	0.03	0.50–0.82	≤/≥238.0	77/53
LVESV, ml	0.74	0.001	0.62–0.86	</≥112.0	74/65
LVEF, %	0.49	0.92	0.32–0.66	N/A	N/A
SCD					
LV mass, g	0.83	<0.001	0.73–0.92	≤/≥232.0	77/76
LVESV, ml	0.64	0.07	0.49–0.79	</≥117.0	74/47
LVEF, %	0.82	<0.001	0.73–0.91	</≥29.0	82/71
Pump failure death					
LV mass, g	0.66	0.03	0.50–0.82	≤/≥238.0	77/53
LVESV, ml	0.74	0.001	0.62–0.86	</≥112.0	74/65
LVEF, %	0.49	0.92	0.32–0.66	N/A	N/A

CI = confidence interval; ROC = receiver-operating characteristic; other abbreviations as in Table 1.

when patients were grouped according to sudden or non-sudden cardiac death.

**EOB and SCD prediction.** In CHF, EOB occurs in a percentage that ranges between 12% and 30%, according to different criteria used to classify oscillatory pattern and its features (15,16,24). The EOB prevalence in our patient population was 33% and, remarkably, it was present in all cases of SCD.

Data provided by the landmark study by Mancini et al. (7) showed that among patients who were deferred from heart transplantation because of a peak  $\text{VO}_2 \geq 14 \text{ ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ , mode of death was sudden in all cases. Consistently, in the present study, performed in the beta-

blocker era, average peak  $\text{VO}_2$  was similar to Mancini's population in both cases of SCD and pump failure deaths, reinforcing the information that SCD might occur also in patients with a “non-prognostic” peak  $\text{VO}_2$ .

Most of the recent literature highlights exercise  $\text{VE}/\text{VCO}_2$  slope as the reference prognostic marker in CHF (9–14,17,18). In the present study,  $\text{VE}/\text{VCO}_2$  slope was not actually predictive of SCD but emerged as the strongest independent marker of cardiac pump failure events. Nonetheless, a large number of patients (59%) who died of SCD exhibited a high  $\text{VE}/\text{VCO}_2$  slope, implying that a further note of attention to preventive strategies and clinical decision-making is advisable when both abnormal ventilatory features are present.

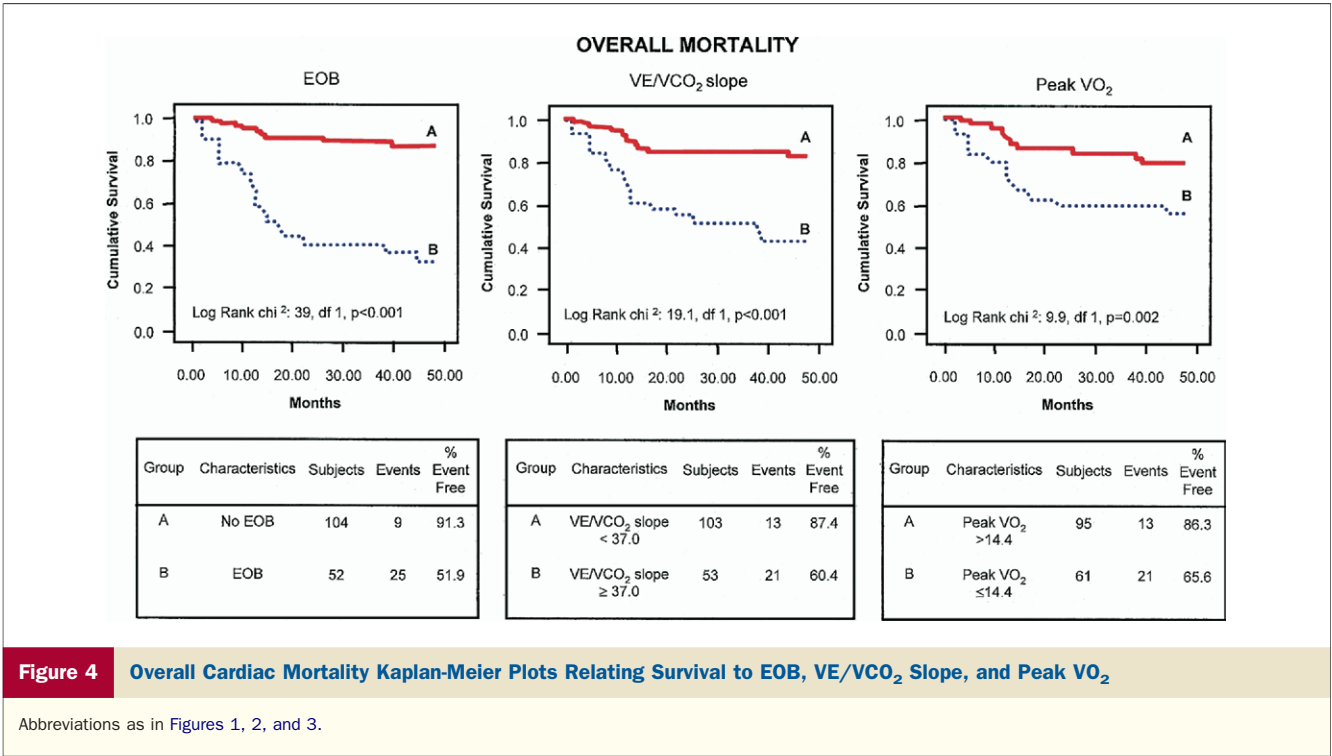
The mechanisms responsible for EOB might well be multifactorial, but, in principle, an instability in feedback peripheral and central chemoreflex control of ventilation can be involved (19,25). The link between these abnormalities and multiple aspects of the pathophysiology of heart failure syndrome lends support to the EOB's remarkably superior value in the clinical assessment of the whole spectrum of CHF patients (15,16,24) and to its special meaning in predicting SCD. Specifically, an impaired chemosensitivity, which might even occur in the early stages of heart failure disease or in the presence of a quite preserved exercise performance, is related to severe autonomic imbalance with increased sympathetic activation (26,27) and high prevalence of ventricular arrhythmias (28,29) and is, per se, an independent prognostic marker (18). It is tempting to speculate on the potential reasons whereby, despite similar and interdependent pathways that are postulated to be common in both increased  $\text{VE}/\text{VCO}_2$  slope and EOB (19), the latter emerges as the reference CPET predictor of SCD.

As recently demonstrated by other authors (24), EOB is associated in a very high percentage of cases with sleep-disordered breathing, namely with sleep apnea of central origin. This important association might suggest that EOB is a clinical manifestation whose pathophysiological background recognizes a more severe state of demodulated

**Table 4** Univariate Cox Regression Analysis

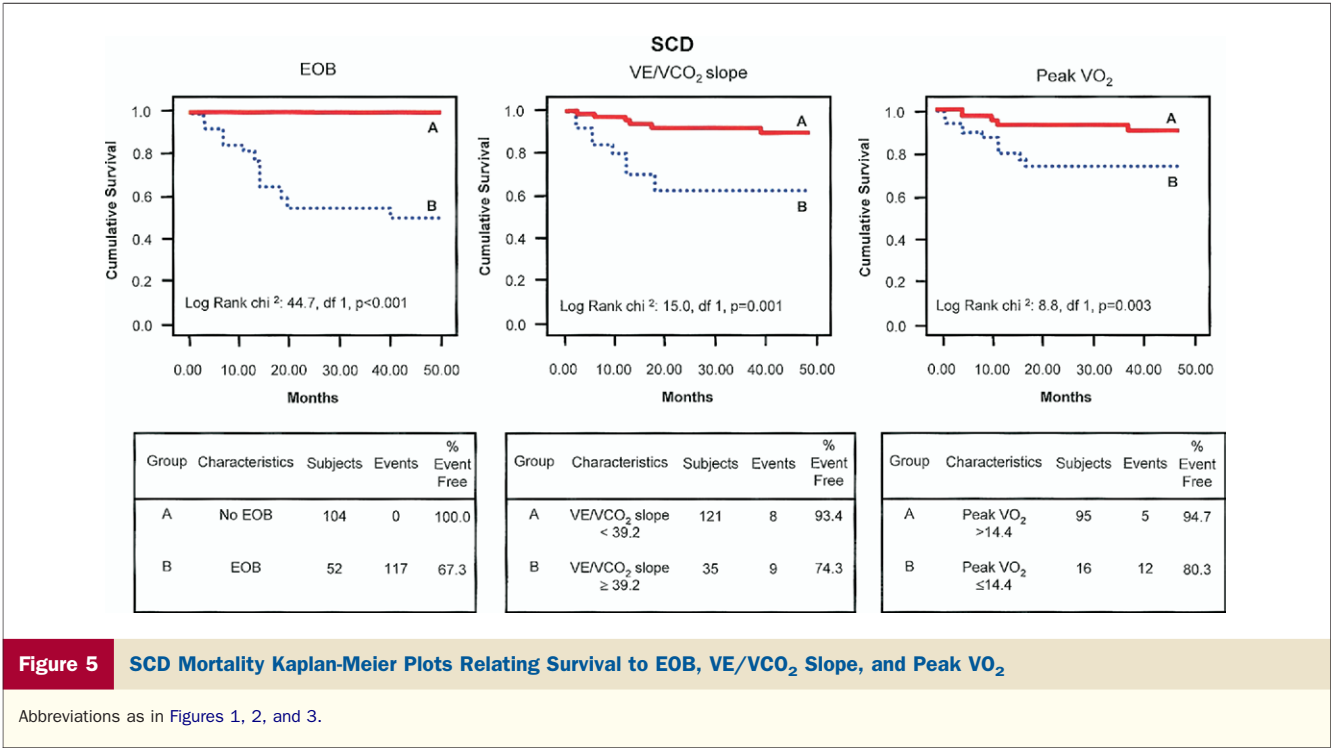
	Chi-Square	Hazard Ratio	95% CI
Overall cardiac mortality			
Peak $\text{VO}_2$	9.8*	2.9*	1.4–5.8
$\text{VE}/\text{VCO}_2$ slope	19.0†	4.1†	2.1–8.3
EOB	38.7†	7.9†	3.7–17.0
LV mass	37.3†	6.8†	3.3–13.8
LVESV	31.5†	6.1†	3.0–12.5
LVEF	8.2*	2.6*	1.3–5.3
SCD			
Peak $\text{VO}_2$	8.8*	4.3*	1.5–12.1
$\text{VE}/\text{VCO}_2$ slope	14.9*	5.4*	2.1–14.1
EOB	39.6†	45.4†	6.0–34.3
LV mass	28.3†	11.4†	3.7–35.0
LVESV	9.3*	4.2*	1.5–11.2
LVEF	17.7†	6.9†	2.4–19.6
Pump failure death			
Peak $\text{VO}_2$	7.5‡	3.5‡	1.3–9.1
$\text{VE}/\text{VCO}_2$ slope	11.8*	4.9*	1.8–13.3
EOB	4.3‡	2.7‡	1.0–6.9
LV mass	12.7†	4.9*	1.9–12.7
LVESV	28.1†	10.6†	3.7–30.1
LVEF	0.12	N/A	N/A

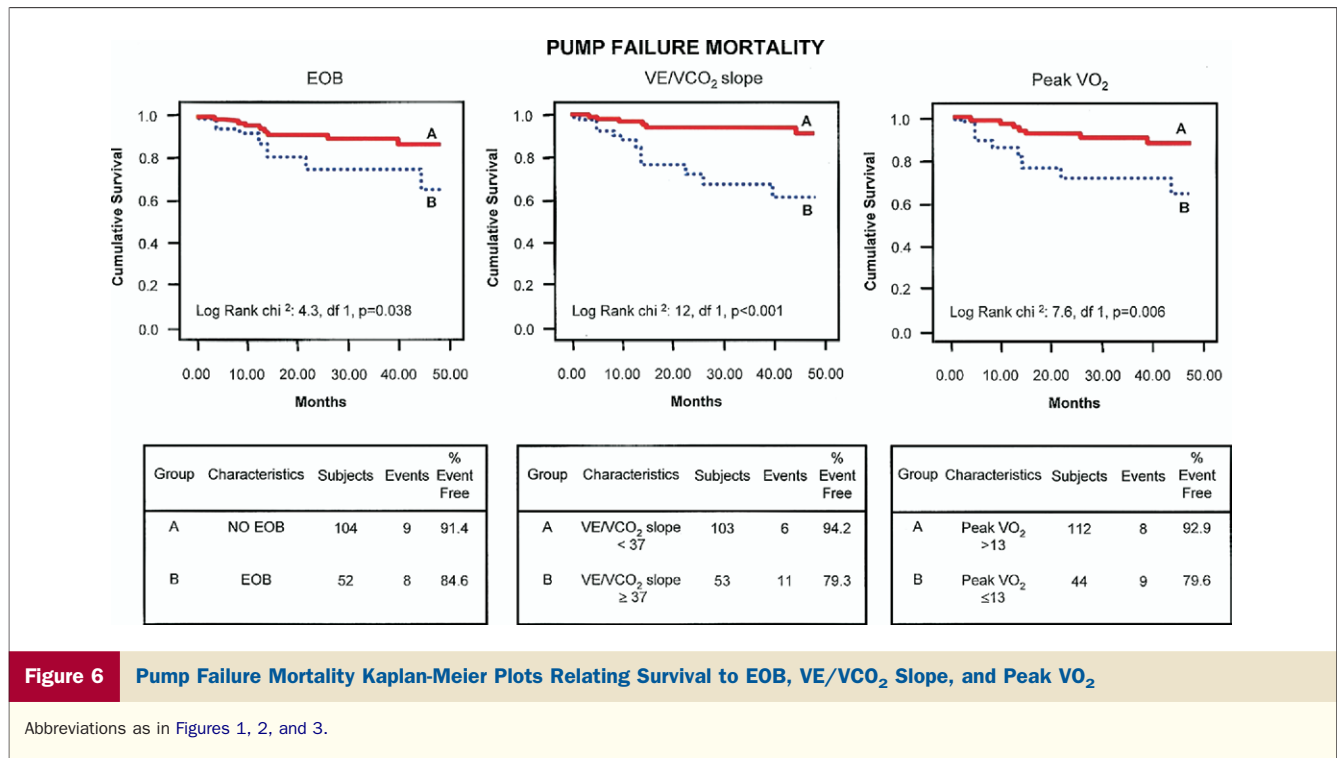
\*p < 0.01; †p < 0.001; ‡p < 0.05.  
Abbreviations as in Tables 1, 2, and 3.



neural reflexogenic control causing ventilation instability. Accordingly, it might be hypothesized that patients with EOB are those in whom chemoreflex overactivity, activation of sympathetic nervous system, and baroreflex impairment are more pronounced, making patients more vulnerable to the occurrence of arrhythmic events. These speculations might be supported or denied by trials specifically designed to identify autonomic and ventilatory control differences in large subgroups of CHF patients with or without EOB, whose breathing pattern is also investigated during sleep.

Furthermore, the relevance of EOB in discriminating SCD risk will be reinforced by studies in CHF populations covering a wide demographic spectrum and a variable range of severity of LV systolic and diastolic dysfunction.





**Study limitations.** The sample size and the relatively small number of events limited the number of variables in our regression model. However, the study was aimed at making a head-to-head comparison among established CPET-derived variables.

Our reported associations were adjusted for known prognostic factors, but we were unable to adjust our findings for other important prognostic indicators, including biomarkers of neurohumoral activation and neural predictors of SCD. Furthermore, despite a similar cardiopulmonary performance in SCD patients, as in the pump failure group—as reflected by average peak VO<sub>2</sub>, peak RER, and VE/VC<sub>2</sub> slope—LVEF was significantly lower (25% vs. 35%; *p* < 0.05) and LVESV and LV mass were significantly greater in SCD. In this regard, at multivariate analysis, LV mass showed a high prognostic predictivity for overall cardiac mortality and, consistent with findings from Framingham study, for SCD (30). The LVESV strongly predicted pump failure death and not SCD.

However, owing to the relatively limited number of deaths, we could not perform a specific EOB stratification by including LVEF and LV mass. Further work in a larger study cohort is warranted to determine whether EOB is independently associated with mortality after adjustment for these other known prognostic markers. Additional data on the eventual association between EOB and hospital stays for CHF are also needed. The SCD patients were receiving beta-blocker therapy in a lower percentage of cases compared with survivors and pump failure patients. This was due to the greater number of cases in NYHA functional class IV, who were intolerant to even lower drug titration

doses. Nonetheless, in a quite high rate of cases, SCD patients were receiving spironolactone, a drug whose anti-failure benefits might well translate into an antiarrhythmic effect and prevention of SCD (31). Another main point that needs critical and cautious evaluation is the theoretical implication of using EOB as a marker for prioritization to ICD implantation. In fact, reasoning on our numbers only, one-third of patients would get benefit from ICD on the basis of an EOB diagnosis. Specifically, at 2 years' follow-up for every 100 HF patients, 78 will survive and 22 will die from pump failure or SCD. Among survivors, 17 will have EOB. Because the number of SCD is only 11% of the total, even though all were associated with EOB, it amounts to an absolute number of 11 patients/100 with HF. Also, by the same calculation, 11 pump failure deaths/100 CHF patients would be expected and 47% (5) will have EOB. Thus, the total number of patients with EOB (per 100 CHF patients) comes to 33; however, only 11 among the whole EOB population would eventually get benefit from the device. On the basis of these considerations, proposal of ICD implantation simply on this particular data set does not seem advisable. This, of course, points out the complexity of the problem, which involves ethical as well as financial issues, problems that are well behind the scope of this investigation.

**Conclusions**

Exercise oscillatory breathing has emerged as a possibly independent predictor of SCD in patients with CHF as well as a promising additional marker for determining which



**Table 5** Multivariate Cox Regression Analysis

Overall Cardiac Mortality		
Variable	Chi-Square	p Value
EOB	38.7	<0.001
Residual Chi-Square		
LV mass*	13.5	<0.001
VE/VCO <sub>2</sub> slope*	7.9	0.005
LVESV*	6.3	0.01
Peak VO <sub>2</sub>	0.83	0.36
LVEF	0.61	0.44
SCD		
Variable	Chi-Square	p Value
EOB	44.7	<0.001
Residual Chi-Square		
LV mass*	10.5	0.001
LVEF	2.5	0.11
Peak VO <sub>2</sub>	2.4	0.12
LVESV	0.45	0.50
VE/VCO <sub>2</sub> slope	0.74	0.39
Pump Failure Death		
Variable	Chi-Square	p Value
LVESV	28.1	<0.001
Residual Chi-Square		
VE/VCO <sub>2</sub> slope*	9.6	0.002
LV mass*	4.1	0.04
LVEF	1.1	0.27
EOB	0.95	0.33
Peak VO <sub>2</sub>	0.60	0.44

\*Variable retained in multivariate regression.  
Abbreviations as in Tables 1 and 2.

patients deserve prioritization to antiarrhythmic strategies and eventually ICD implantation. To confirm and expand these findings, additional trials in large CHF populations are needed.

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